FRESH FROM THE PIPELINE

Velaglucerase alfa

Johannes M. F. G. Aerts, Uma Yasothan and Peter Kirkpatrick

In February 2010, velaglucerase alfa (Vpriv; Shire) was approved by the US Food and Drug Administration as a long-term enzyme replacement therapy for paediatric and adult patients with type 1 Gaucher's disease. It was granted marketing authorization by the European Commission for the same indication in August 2010.

Gaucher's disease is a rare genetic disorder caused by mutations in the gene that codes for the lysosomal enzyme β-glucocerebrosidase, which catalyses the metabolism of the sphingolipid glucocerebroside[1]. Owing to the resultant deficiency in β-glucocerebrosidase activity, glucocerebroside accumulates, primarily in the lysosomal compartment of macrophages[1]. The presence of such cells in the bone marrow and the spleen leads to anaemia and thrombocytopenia, and their accumulation in the liver and the spleen results in the enlargement of these organs[1].

Basis of discovery

Before the 1990s, treatment of Gaucher's disease was palliative, involving interventions, such as splenectomy. Although enzyme replacement therapy (ERT) for lysosomal storage disorders, such as Gaucher's disease, was proposed in the 1960s, producing sufficient quantities of β-glucocerebrosidase and targeting it to the appropriate cells proved challenging[2]. Based on an understanding of the importance of the mannose receptor on the surface of macrophages in enzyme internalization, placenta-derived β-glucocerebrosidase, processed to expose mannose chains to promote recognition by macrophages, was developed[2,3]. Injection of such a β-glucocerebrosidase product, alglucerase (Ceredase; Genzyme), improved key disease characteristics, such as low haemoglobin concentrations in patients with Gaucher's disease[2,3], which led to its approval by the US Food and Drug Administration (FDA) in 1991.

ERT is now the standard of care for symptomatic type 1 Gaucher's disease[1,2]. Imiglucerase (Cerezyme; Genzyme), a recombinant analogue of β-glucocerebrosidase produced in Chinese hamster ovary cells[2,4], was approved by the FDA in 1994 and largely replaced alglucerase. In addition, miglustat (Zavesca; Actelion), a small-molecule drug that inhibits the synthesis of sphingolipids, such as glucocerebroside[1], was approved by the FDA in 2003 for patients with mild to moderate type 1 Gaucher's disease for whom ERT is not an option.

Drug properties

Velaglucerase alfa, which is produced by gene-activation technology in a human fibroblast cell line, has the same amino-acid sequence as human glucocerebrosidase[5–7]. It is manufactured to contain predominantly high mannose-type *N*-linked glycan chains at the four occupied *N*-glycosylation sites to facilitate internalization of the enzyme mediated by the mannose receptor on target cells[5–7]. Velaglucerase alfa catalyses the hydrolysis of glucocerebroside to glucose and ceramide, reducing the amount of accumulated glucocerebroside[5–8].

Clinical data

The efficacy of velaglucerase alfa (administered intravenously over 60 minutes every other week) was evaluated in three clinical trials involving a total of 99 patients with type 1 Gaucher's disease[6,7].

Two randomized, double-blind trials involved patients with Gaucher's disease-related anaemia and either thrombocytopenia or organomegaly who were not currently receiving specific therapy for Gaucher's disesase[6,7]. One of these studies was a 12-month trial involving 25 patients aged 4 years and older who were naive to ERT (defined as having not been treated with ERT for at least 30 months before study entry)[6,7]. Patients were randomized to receive velaglucerase alfa at a dose of either 45 units per kg or 60 units per kg every other week[6,7]. In both groups of patients, the mean change in haemoglobin concentration from baseline — the primary end point — was 2.4 g per decilitre, which is considered to be a clinically meaningful increase[6,7,9]. In addition, in the group that received the 60 units per kg dose, the mean reduction in liver volume was 17%, the mean reduction in spleen volume was 50% and platelet count increased by 51×10^9 per litre[6,7]. The corresponding changes in the group that received the 45 units per kg dose were a 6% mean reduction in liver volume, a 40% mean reduction in spleen volume and an increased platelet count of 41×10^9 per litre[6,7].

The second study was a 9-month randomized, double-blind, non-inferiority trial involving 34 patients aged 3 years and older who were not allowed to have received disease-specific therapy for at least the previous 12 months[6,7]. Patients were randomized to receive either 60 units per kg of velaglucerase alfa or 60 units per kg of imiglucerase every other week[6,7]. After 9 months of treatment, the mean absolute increase from baseline in haemoglobin concentration for patients treated with velaglucerase alfa was 1.6 g per decilitre[6,7]. This was clinically and statistically non-inferior to that observed with imiglucerase; the mean treatment difference in change from baseline to 9 months (velaglucerase alfa minus imiglucerase) was 0.1 g per decilitre[6,7]. There were no statistically significant differences between the groups receiving velaglucerase alfa and imiglucerase in the changes in platelet counts and liver and spleen volumes after 9 months of treatment, and in the time to first haemoglobin response (defined as 1 g per decilitre increase from baseline)[6,7].

A third 12-month open-label, single-arm trial involved 40 patients aged 9 years and older who had been receiving treatment with imiglucerase at doses ranging between 15 units per kg to 60 units per kg for a minimum of 30 consecutive months[6,7]. Patients were also required to have a stable biweekly dose of imiglucerase for at least 6 months before enrolment[6,7]. Imiglucerase therapy was stopped and treatment with velaglucerase alfa was administered every other week at the same number of units as the patient's previous imiglucerase dose[6,7]. Haemoglobin concentrations and platelet counts remained stable on average throughout the 12 months of treatment with velaglucerase alfa and no patient required dosage adjustment during this period[6,7].

Indications

Velaglucerase alfa is approved by the FDA as a long-term ERT for paediatric and adult patients with type 1 Gaucher's disease[6]. It is approved by the European Commission as a long-term ERT in patients with type 1 Gaucher's disease[7]. ▸

ANALYSIS | GAUCHER'S DISEASE

Analysing issues for the treatment of Gaucher's disease is Johannes Aerts, M.D., Professor at the Department of Medical Biochemistry, Academic Medical Center, University of Amsterdam, The Netherlands.

The approval of velaglucerase alfa has provided a welcome additional ERT for Gaucher's disease. An obvious question is the comparative efficacy of velaglucerase alfa with imiglucerase. With regard to chemical composition, velaglucerase alfa has the same amino-acid sequence as human β-glucocerebrosidase, whereas imiglucerase contains a histidine at residue 495 rather than an arginine[5]. In addition, the overall *N*-linked glycan composition of the two products differ, with velaglucerase alfa largely having natural high-mannose-type oligosaccharides, whereas the glycans in imiglucerase have been enzymatically trimmed to $(Man)_3(GlcNac)_2$ structures[5]. Despite these differences, clinical studies have so far not shown major differences between the two enzymes with respect to pharmacokinetics and efficacy[4,8,10]. In addition, a recent study that systematically compared the two enzymes in a mouse model of Gaucher's disease concluded that both enzymes show similar therapeutic effects at several different doses and at different ages, with differing degrees of disease involvement[11].

Since the summer of 2009, there has been a global shortage of imiglucerase for the treatment of Gaucher's disease owing to viral contamination of Genzyme's production facility, which necessitated its temporary shutdown. This shortage has led to either the interruption of treatment, dose reduction or the starting of alternative treatments[12]. Initial reports[13,14] of the effects of treatment withdrawal in adult patients with stable disease suggest that, when appropriately monitored, some patients may safely interrupt treatment for a short period of time because irreversible complications are unlikely to occur in a couple of months. Alternatively, some patients have been switched to miglustat (the oral substrate reduction therapy) or to other ERTs — either velaglucerase alfa or taliglucerase alfa (developed by Protalix, which is produced in plant cells[15]) — that have been made available through expanded access programmes. The collection of information on each patients' well being and their disease parameters following treatment switches is of utmost importance, which may be best achieved by creating an independent database of clinical assessments and standardized laboratory measurements, such as markers for Gaucher's storage cells[16,17].

The availability of taliglucerase alfa is eagerly awaited and it is hoped that this enzyme will be comparatively effective and increase the choice between treatment modalities. It is also hoped that the use of a plant-cell production system could lead to considerable price reductions, as the high costs associated with ERT are a limitation on its use in some countries. The development of an alternative small-molecule compound for oral substrate reduction therapy, eliglustat tartrate, by Genzyme is also exciting. The compound seems to be safe and well tolerated[18], and a 2-year follow-up of a Phase II trial indicated major improvements in haematological, visceral and skeletal manifestations in adult patients with type 1 Gaucher's disease, on a par with ERT[19]. Moreover, as ERT is not able to prevent or treat neurological abnormalities in severely affected patients because the enzymes are unable to pass the blood–brain barrier, such compounds could provide a much needed treatment option for these patients.

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Box 1 | The market for drugs for Gaucher's disease

Analysing the market for Gaucher's disease is Uma Yasothan, IMS Health, London, UK.

The global market for drugs for Gaucher's disease is estimated to be worth ~US$475 million annually, of which the European Union (EU) represents ~45%[20]. The approved treatments for Gaucher's disease include the enzyme replacement therapy (ERT) imiglucerase (Cerezyme; Genzyme), the market leader, which is estimated to be responsible for ~90% of the market, and the small-molecule drug miglustat (Zavesca; Actelion). Velaglucerase alfa (Vpriv; Shire), another ERT, was granted marketing authorization for type 1 Gaucher's disease in the EU in August 2010 and was launched in the United States at the beginning of 2010. Vpriv offers the first alternative ERT to Cerezyme, which was launched nearly two decades ago. Manufacturing issues for Cerezyme since 2009 have provided an opportunity for Vpriv to gain market share. However, further competition is imminent from another ERT, taliglucerase alfa (developed by Protalix/Pfizer), which is undergoing FDA review. Analysts predict that sales of Vpriv will be ~$50 million in 2010, rising to $260 million in 2015 (REF. 21).

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Competing financial interests

J.M.F.G.A declares competing financial interests: see web version for details.